REMARKS

Claims 1-6 and 9-10 are amended. Claims 7-8 and 11 are canceled. Claims 12 and 13 are added as new claims. Support is found, for example, in the original claims. No new matter is presented.

I. PTO 892 Form

Applicants note that the Vosper reference mentioned at page 8 of the Action was omitted from the PTO 892 Form. Applicants respectfully request the Examiner to include a PTO 892 Form listing the Vosper reference with the next Action for the record.

II. Priority

The Examiner has acknowledged receipt of *some* of the priority documents submitted under 35 U.S.C. § 119(a)-(d). However, Applicants note that certified copies of both Japanese priority applications, Nos. JP 2003-330616 and JP 2004-23546 have been submitted and received by the U.S. PTO as evidenced by the Image File Wrapper (IFW) for the above-identified application on the PTO's PAIR website. A copy of the list of documents available in the IFW for the above-identified application and the front page of each of the Japanese priority applications printed from the IFW are attached for the Examiner's convenience as Attachment 1.

Regarding the Examiner's statement that the claimed benefit to an earlier priority date is denied because Applicants have not provided a certified translation of the priority documents, Applicants consider note that the Examiner's intention to use "some" might be to indicate that an English translation of the priority documents were not submitted, rather than literally meaning that all of the certified copy of the priority documents were not received. However, for the

record, Applicants are not required to submit certified English translations of the priority documents, unless Applicants intend to rely on the priority documents to overcome a reference.

In view of the above, Applicants respectfully request the Examiner to formally acknowledge receipt of *all* of the certified copies of *all* of the priority documents in the next Action for the record.

The Examiner is correct in that the effective U.S. filing date of the present application is September 21, 2004, which is the filing date of the international application, to the extent that certified English translations of the Japanese application priority documents have not been submitted.

III. Response to Claim Rejection under 35 U.S.C. § 112, 2nd Paragraph

Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the term "medicament" is unclear.

Claim 9 is amended herein to recite "a pharmaceutical composition", thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection.

IV. Response to Claim Rejections under 35 U.S.C. §, 1st Paragraph

A. "Solvates" and "prodrugs"

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, allegedly does not reasonably provide enablement for making "solvates" of the claimed compounds.

The claims are amended herein by deleting the terms "solvates" and "prodrugs", thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection.

B. PPAR-mediated diseases

Claims 6-10 are additionally rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement allegedly because the specification does not enable the instant compounds to treat any and all known or unknown PPAR-mediated diseases. The Examiner does indicate that the claims are enabled for the PPARδ-mediated disease hyperlipidemia.

Claims 6 is amended herein to recite that the pharmaceutical composition is a therapeutic agent for hyperlipidemia or adiposity and claim 10 is amended to recite a method of treatment for hyperlipidemia or adiposity. As noted above, the Examiner states that the claims are enabled for hyperlipidemia. Applicants further submit that the claims are also enabled for the treatment of adiposity based on the following.

The present specification teaches that the compounds of the present invention have PPARδ activity and that it has been reported that compounds, which possessed high affinity to PPARδ protein and which could activate PPARδ significantly (i.e., agonists) were found to have HDL (high density lipoprotein) cholesterol level-elevating activity and non-HDL cholesterol level-lowering effect. It is further disclosed that it was found that macrophages introduced oxidized LDL, their foam occurred and they deposited into vascular endothelium to cause lipid metabolic disease. Therefore, agonists that can activate PPARδ reduce foam cells by HDL cholesterol level-elevating effect and LDL cholesterol level-lowering effect and so they are expected to be useful for preventive and/or therapeutic agent of lipid metabolic disorder (*e.g.* hyperlipidemia (hypercholesterolemia, hypo-HDL-cholesterolemia, hyper-LDL-cholesterolemia,

hypertriglyceridemia *etc.*), atherosclerosis, cardiovascular disease, adiposity, metabolic syndrome *etc.*), hypertension, circulatory diseases *etc.* It is also disclosed in the specification that activation of PPARδ increased fatty acid oxidation especially in skeletal muscles, which also suggests that PPARδ agonists are useful for the improvement of lipid metabolic disorder and therapy of adiposity. In view of the description in the specification which establishes that the compounds of the present invention activate PPARδ and that PPARδ agonists are useful for the improvement of lipid metabolic disorder and therapy of adiposity due to their ability to reduce foam cells by HDL cholesterol level-elevating effect and LDL cholesterol level-lowering effect and due to their ability to increase fatty acid oxidation especially in skeletal muscles, Applicants submit that the specification is enabling for the treatment of both hyperlipidemia and adiposity.

In view of the above, Applicants submit that present claims 6 and 10 are sufficiently enabled based on the knowledge and skill available in the art and the guidance provide in the specification.

Claims 7 and 8 are canceled herein, thereby rendering the rejection moot as to these claims.

Applicants respectfully traverse the rejection with respect claim 9 as claim 9 does not recite treatment of PPAR-mediated diseases.

Accordingly, Applicants respectfully request withdrawal of the rejection.

C. "Prevention"

Claims 6-10 are rejected under 35 U.S.C. § 112, 1st paragraph, allegedly because the specification does not reasonably provide enablement for preventing diseases. The Examiner suggests deletion of the word prevention.

Claims 6 and 10 are amended herein by deleting references to "preventive" or "prevention", thereby obviating the rejection.

Claims 7 and 8 are canceled herein, thereby rendering the rejection moot as to these claims.

Applicants respectfully traverse the rejection of claim 9 as claim 9 does not recite "prevention".

Accordingly, Applicants respectfully request withdrawal of the rejection.

V. Response to Claim Rejections - 35 U.S.C. §102

Claims 1-2, 4 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tajima et al WO 99/46232 ("WO '232").

Claims 1 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brooks et al WO 2001/016120 ("WO '120").

Claims 1 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cheng et al WO 2002/096358 ("WO '358).

Claims 1-2 and 4-5 are rejected under 35 U.S.C. § 102(e) as being anticipated by Conner et al WO 2003/072102 ("WO '102").

Applicants respectfully traverse the rejection with respect to claim 4 as none of the cited references discloses a specific compound identical to any one of the compounds recited in claim 4 as filed. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim 1 is amended herein by incorporating the subject matter of original claim 3, which is not included in the rejections. That is claim 1 is amended to recite that ringA represents 4-(trifluoromethyl)piperidin-1-yl, 2,2-difluoro-1,3-benzodioxol-5-yl or 3,4-dihydro-1H-

isoquinolin-2-yl. None of the cited references discloses compounds within the scope of amended claim 1. Specifically, in view of the amendment to claim 1, the specific compounds identified by the Examiner as described in WO '232 are not included in compounds of formula (I) as recited in amended claim 1. Similarly, in the compounds described in WO '120, WO '358 and WO '102, rings corresponding to ringA in the present claims are benzene or pyridine. Therefore, the compounds described in the these publications are not included in the compounds of formula (I) as recited in amended claim 1. Thus, claim 1 is not anticipated. Claims 2-5 depend from claim 1 and are not anticipated for at least the same reasons.

Accordingly, Applicants respectfully request withdrawal of the §102 anticipation rejection.

VI. Response to Claim Rejections - 35 U.S.C. §103

Claims 1-2 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Conner et al, WO '100. The Examiner's position is that the compounds disclosed by WO '100 have a close structural similarity to the compounds of the present claims as homologues.

As set forth above, claim 1 is amended herein to recite that ringA represents 4-(trifluoromethyl)piperidin-1-yl, 2,2-difluoro-1,3-benzodioxol-5-yl or 3,4-dihydro-1H-isoquinolin-2-yl and WO '100 does not disclose compounds within the scope of amended claim 1. Specifically, the corresponding ring in WO '100 with ringA in formula (I) in claim 1 in the present application is limited to six-membered unsaturated rings such as benzene or pyridine. Furthermore, in the definition of substituents in the six-membered unsaturated rings, there is no description that the substituents form fused rings with the six-membered unsaturated rings.

Moreover, WO '100 fails to provide any data showing that the compounds described therein are PPARα selective agonist or PPARδ selective agonist.

On the other hand, among the rings representing ringA in formula (I) in claim 1 in the present application, 4-(trifluoromethyl)piperidin-l-yl and 3,4-dihydro-IH-isoquinolin-2-yl are saturated rings which necessarily include nitrogen, which is different from the compounds in WO '100. Thus, WO '100 does not teach, suggest or even recognize the advantageous effects of claimed compounds of formula (I) which have a particular structure of ringA. One skilled in the art would not have been able to recognize the importance of the structure of ringA, and thus would not have been motivated to select or modify the structure of ringA of WO '100 to reach the claimed invention.

In support of the above, Applicants submit comparative experimental data attached herewith as Attachment 2, which shows that selectivity of PPARδ increases significantly by changing rings corresponding to ringA from an unsaturated ring to a saturated ring. In the comparative experiment, the compound of Example 34 (11) in the present application and the compound in Example 2-133 in WO '232, which is the most similar compound to the inventive compound of Example 34(11), are used. This is because when ringA is 2,2-difluoro-1,3-benzodioxol-5-yl in formula (I) of the present application the compounds of WO '232 are considered to be closer to the present compounds than the compounds of WO '100. Additionally, in the definition of the substituents of benzene in formula (I) of WO '100 corresponding to ringA in the present claims, although R6 is hydroxy(C 1-C3)alkyl, R7 and R8 are not hydroxy(C1-C3)alkyl. Therefore, since benzodioxol can not be formed in the compounds

of WO '100, it is not obvious that PPARδ selectivity increases by changing ring A to be benzodioxol.

Specifically, as described in the "Disclosure Of The Invention" section in the present specification, the compound in Example 26 in the present application has a structure wherein the combination of each of the substituents, which is not described in WO '232, and the position thereof is preferably selected in order to have selectivity as PPARδ agonist among three PPAR isoforms: α, γ and δ and avoid side effects which are concerned by activation of other PPAR isoforms, especially hepatotoxicity. As shown by the attached comparative experimental data, the compound in WO '232 (Example 2-96) which is closest to the compound in the present application has inadequate PPARδ selectivity and inadequate rat PPAR isoforms selectivity. Therefore, the compound is not adequate as a pharmaceutical since there is possibility that the compound has toxicity in safety test in rats.

On the other hand, the compound in Example 26 in the present application has increased selectivity of PPARδ and adequate rat PPAR isoforms selectivity in comparison with the compound in WO '232. Thus, the compound in Example 26 in the present application can avoid side effects.

As described above, the compounds in the present application, are unobvious from the cited references.

Accordingly, Applicants respectfully request withdrawal of the §103 rejection.

VII. New Claims 12 and 13

New claims 12 and 13 are directed to specific compounds of the present invention.

The compounds recited in new claim 12 correspond to the compound of Example 34(11) (compound 13 in original claim 4), which has a 3,4-dihydro-1H-isoquinolin-2-yl ring corresponding to ringA and the compound of Example 33 (compound 8 in original claim 4), which has a 4-(trifluoromethyl)piperidin-1-yl ring corresponding to ringA.

The compound recited in new claim 13 corresponds to Example 26 (compound 5 in original claim 4), which has a 2,2-difluoro-1.3-benzodioxol-5-yl ring corresponding to ringA in formula (I).

These compounds are not specifically disclosed or suggested by the cited references for the reasons set forth above.

VIII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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Date: August 6, 2008